PLATEAU IN MUSCLE BLOOD FLOW DURING PROLONGED EXERCISE IN MINIATURE SWINE

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Report No. 88-32, supported by the U. S. Army Nutrition Task Force (Work Unit #141) and U. S. Navy Medical Research and Development Command. The views presented in this paper are those of the authors and do not reflect the official policy or position of the Department of the Navy, the Department of Defense, or the U. S. Government.

SUMMARY

Muscle blood flow remained unchanged during prolonged exercise when pigs were cooled by skin wetting and a fan. This muscle blood flow response was comparable to that of humans exercising under similar conditions. The effect of temperature on this response is uncertain since both increases and decreases in muscle blood flow have been reported during thermal stress. Swine were similar to humans in regulating blood flow distribution during prolonged exercise. Cardiovascular drift in swine differs from that in humans due to difference in temperature regulation, posture and maintenance of central blood volume. The upward drift in heart rate and cardiac output during prolonged exercise was probably the result of increasing skin blood flow and sympathetic drive. Upward drift in oxygen consumption in animals has not been well demonstrated, but our results tend to support the known contributing factors in humans. Further work is needed to determine the role of temperature and exercise intensity on the muscle blood flow response to prolonged exercise.

INTRODUCTION

Prolonged exercise challenges the systemic regulation of metabolism, blood flow and temperature. Previous studies in rats and miniature swine have suggested that muscle blood flow progressively increases over time during prolonged treadmill exercise (3,4,23). Cardiac output matched this progressive time dependent response for the swine (3). In contrast, humans have exhibited a relatively constant muscle blood flow (1) and cardiac output (9) when exercising in a thermoneutral environment at a fixed intensity. These contrasting findings may be partially attributed to differences in natural capacity for thermoregulation.

Core temperature has been shown to increase in proportion to the duration and intensity of exercise and the environmental heat load in humans (29,32). Blood flow was redistributed to the skin during prolonged exercise to support heat loss by sweating (32). This resulted in a cardiovascular drift (CVD) that has been described as a progressive decline in central blood volume, stroke volume and mean arterial pressure along with an upward drift in heart rate (5-15%), and an unchanged cardiac output (9). Thermoregulatory mechanisms associated with CVD resulted in a modest upward drift in core temperature (1-1.5^{o}C) that reached a plateau after 30 minutes of exercise (9,29).

In contrast, non-sweating animals have limited avenues for heat dissipation during exercise. This has been demonstrated by the marked increases in core temperature that have occurred during prolonged exercise in both rats and pigs (3,12). In pigs, a progressive 2.5^{o}C increase in colonic temperature during 30 minutes of treadmill exercise was associated with 25% (62 b·min^{-1}) and 22% increases in heart rate and cardiac output, respectively (3). These results describe the greater thermal and cardiovascular stress and characteristically different CVD during exercise for the pig compared to humans. Furthermore, cooling miniature swine by skin wetting and a fan has limited the increases in core temperature and heart rate during prolonged runs of up to five hours in duration (26). These observations suggest that increases in core temperature were a principle determinant of the increases in cardiac output and muscle blood flow during prolonged exercise in swine (3). A suggestion that contradicts reports on sheep (5) and humans (32).

Therefore, the purpose of this investigation was to further examine the role of core temperature in the regulation of central hemodynamics and regional blood flow during prolonged exercise. This study focused on

muscleblood flow responses to prolonged treadmill exercise. A more detailed description of splanchnic blood flow responses has been presented in a separate publication (13).

METHODS

Animal Subjects. Eight male miniature swine (51 ± 12 kg, X±SD; 9-12 months old) served as subjects for this investigation (Yarshire strain, Riggs Piggs, Ramona, CA). Animals were housed individually in a facility approved by AALAC and the USDA. Pig chow was given twice daily for a total intake of 4% of body weight. Water intake was ad libitum.

Exercise Training Protocol. Animals were familiarized with treadmill exercise for two weeks prior to the initiation of exercise training. Treadmill familiarization progressed from low speed walking to slow running for 10 minute periods on three alternate days per week (MWF). Two maximal exercise tests (MXT) were used to establish the pre-training exercise capacity and maximal heart rate (HR) response. Training intensity was set at 65% of the maximum HR reserve [HR_{rest} +.65 (HR_{max} - HR_{rest})]. Animals were trained five days per week beginning with 20 min/day during week one and progressing to 60 min/day by week six. Thereafter, animals trained 60 min/day, three to four days per week with a shorter 30 min exercise bout on Wednesday. The appropriate training intensity was maintained by weekly heart rate monitoring and adjustment of the treadmill workload to correct for training adaptations. Animals were cooled with a fan and water spray throughout the training runs. Prior to surgery, duplicate MXTs were conducted on separate days to ascertain the effects of training. Post-surgery, animals were permitted to recover four to five days before initiating a re-training protocol. Re-training began with 10 minutes of slow walking and progressed to 30 minutes of regular training after week one. The 60 minute duration was achieved by the end of week two and continued into week three. MXTs were repeated at the end of week three to ascertain the state of training. Exercise experiments were conducted during the fourth week following surgery.

Maximal Exercise Testing (MXT). Animals performed MXTs on a treadmill prior to training, following 8 weeks of training and prior to surgery, and after completing the three week recovery and re-training protocol. The test protocol was designed to elicit a maximal exercise response in approximately 12-15 minutes. The first three stages of 1.9 mph/5% grade, 3.1/5%, and

4.3/5% each lasted three minutes and they were consistent for all tests performed. This permitted an evaluation of submaximal adaptations to exercise training. Subsequently, the treadmill grade was increased by 2.5 or 5% every two minutes until the maximal work load had been achieved. The criteria for determining a maximal response were a plateau in heart rate despite an increase in external workload and/or fatigue as evidenced by an inability of the animal to maintain the work load. The maximal work load was then expressed in watts by the formula: [speed (m/min)]·[(1+(% grade/100))]·[body weight(kg)]·$[6.1]^{-1}$ (6.1 kgm/min = 1 watt). The maximal exercise tests provided determinations of both submaximal and maximal exercise responses.

Surgical Procedures. Anesthesia was induced with ketamine (25 mg/kg) plus atropine (1/60 gr) injected IM followed by sodium thiamylal (20 mg/kg) IV. Following intubation the animal was maintained on 1-2% halothane and oxygen. A left lateral thoracotomy was performed in the fourth intercostal space. Silastic catheters and a temperature port were introduced through the chest wall from exit sites adjacent to the dorsal spine. Two catheters were placed in the descending aorta. A small incision was made in the pericardium and catheters were introduced into the pulmonary artery and left atrium. The temperature port was placed just cranial to the diaphragm and positioned near the apex of the heart. The port was constructed of 2.5 I.D. silastic tubing and sealed at the internal end with silicone adhesive (GE RTV 112). The pericardium was then closed with 3-0 Ethibond (Polybutilate coated Polyester) suture. The chest was closed in layers with 2-0 Vicryl (polyglactin). Catheters were flushed with saline, retained with 1000 units·ml^{-1} heparin and closed with a silk ligature. Sealed catheters were then buried in a subcutaneous pouch adjacent to the spine. A subcuticular stitch (3-0 Vicryl) was used to close all skin incisions. Following three weeks of recovery and re-training the catheters were exteriorized under general anesthesia. The technique of burying catheters subcutaneously for three weeks has proven successful in preventing sinus tract infections and the resulting septicemia. In two animals, catheterization of the aortic root and pulmonary artery was performed by threading silastic and Swan-Ganz catheters into the internal carotid artery and internal jugular vein, respectively. These two animals had previously undergone a laparotomy to catheterize abdominal vessels for dietary studies.

Experimental Protocol. Following a normal recovery from surgery, animals were retrained for three weeks prior to performing the two hour runs. Animals performed the runs at the training intensity of 65% of heart rate reserve following an overnight fast. The treadmill speed and grade ranged from 3.1-3.5 mph and 5 to 10 % grade, respectively. Runs were terminated at exhaustion or the completion of 120 minutes. Animals were sprayed with cool water (18-20°C) every 2-5 minutes and a fan was directed on the animal throughout the run. Room temperatures averaged 20°C dry bulb and 15°C wet bulb. Radiolabeled 15 micron microspheres (Ce_{141}, Cr_{51}, Sn_{113}, Ru_{103}, Nb_{95}, Sc_{46}, In_{114} and Gd_{153}) were injected at rest, 5 minutes, 30 minutes and end exercise for measurement of regional blood flow by the technique of Heymann et al (18). Each injection contained 4 to 5 X 10^6 microspheres to insure that a minimum of 400 microspheres were obtained in each 6 to 8 gram tissue sample obtained at sacrifice. In two animals, microspheres were injected into the aortic root (22). Flow data for the heart, lungs and organs cranial to the aortic injection site were excluded due to poor microsphere distribution in these two pigs. Total gastrointestinal blood flow was determined by cleaning and weighing each organ or region and multiplying that weight times the flow derived from microsphere measurements. Total gastrointestinal flow was derived from the combined flows to the liver, spleen, pancreas, stomach and small and large intestine and then expressed per kilogram body weight. Blood pressure, heart rate, cardiac output, peripheral resistance, core temperature, arterial and mixed venous blood gases, oxygen consumption, and plasma glucose and lactate were determined at rest, 5, 30, 60 and 120 minutes of exercise. Mean arterial pressure was measured with a Statham P23Id transducer and recorded on a Brush 260 recorder. The transducer was zeroed at the level of the left atrium. Systemic vascular resistance was calculated from mean arterial pressure and cardiac output. Heart rate was obtained from a surface bipolar electrocardiogram using a Hewlett-Packard 1511B electrocardiogram recorder. Cardiac output was determined by indicator dilution techniques using the Waters COR-100A cardiac output computer. Indocyanine green (2.5-5 mg) was injected into the left atrium or pulmonary artery while blood was withdrawn from the descending aorta. Computer calibration was performed with a dynamic calibration loop using each animals own blood and an internal reference signal prior to each study. Core temperature was obtained from a Yellow Springs Instruments (YSI) Series 400 thermistor probe inserted

into the temperature port and interfaced with a YSI Model 43 telethermometer. Blood gases and pH were measured on a Radiometer ABL3 and corrected for porcine blood (37). Total body oxygen consumption was derived from the Fick equation using the arterial and mixed venous oxygen contents and cardiac output measurements. Plasma glucose and lactate were measured on a YSI Model 23L glucose/ lactate analyzer. Since dietary manipulation altered blood glucose and lactate concentrations during exercise in two animals, their glucose and lactate data were not included in the analysis.

Statistical Analysis. Paired comparisons were performed using Student's t test. Repeated measures analysis of variance was used for multiple comparisons during the prolonged runs (8). Post hoc comparisons were conducted using Tukeys procedure (38). Multiple regression analysis was performed to identify variables contributing to the variance in the dependent variable. Values are presented as the Mean±Standard Error of the Mean. The minimum level of significance was set at .05 for all comparisons.

RESULTS

Exercise Training Responses. Following surgery and retraining, heart rates at two standard submaximal workloads were reduced by 35 and 38 $b \cdot min^{-1}$, while the relative $watt \cdot pulse^{-1}$ increased by 22 and 66 % in comparison to pretraining values. Peak relative work ($watts \cdot kg^{-1}$) and $watt \cdot pulse^{-1}$ at maximal exercise increased 43 % and 44 %, respectively, when compared to the pretraining responses. The exercise responses post training and following surgery and retraining were not different. These training adaptations enabled the eight animals to run at 65% of the heart rate reserve for 98 ± 7 minutes during the prolonged runs.

Hemodynamics. Cardiac output, heart rate (HR), and mean arterial pressure (MAP) increased and systemic vascular resistance decreased when all exercise means were compared to rest (Table 1, Figure 1). Stroke volume did not change from rest to end exercise. Cardiac output and heart rate increased and systemic vascular resistance decreased from 5 min to the 60 min and end exercise time points. Mean arterial pressure increased from rest but did not change during the exercise bout. The rate pressure product (HR x MAP) at 60 min was elevated above the 5 min value.

Table 1. Hemodynamic and Metabolic Responses to Prolonged Treadmill Exercise.[a]

VARIABLE	REST	EXERCISE 5 min	30 min	60 min	END
VO_2, $ml \cdot min^{-1} \cdot Kg^{-1}$	7.6 ± .4 #	32.8 ± 1.4	33.2 ± 1.6	34.7 ± 2.1	34.3 ± 1.9
Qt, $l \cdot min^{-1}$	5.8 ± .3 #	13.6 ± .8	14.5 ± .8	15.2 ± 1.0 *	15.4 ± 1.1 *
Qt, $ml \cdot min^{-1} \cdot Kg^{-1}$	117 ± 9 #	274 ± 16	292 ± 17	305 ± 21 *	307 ± 19 *
HR, $beats \cdot min^{-1}$	94 ± 6 #	212 ± 5	225 ± 5	229 ± 4 *	232 ± 4 *
SV, $ml \cdot min^{-1} \cdot Kg^{-1}$	1.29 ± .14	1.29 ± .07	1.27 ± .08	1.29 ± .08	1.29 ± .08
a-vO_2, vol%	6.7 ± .5 #	12.1 ± .5	11.5 ± .4	11.4 ± .3	11.2 ± .3 *
Pa, Torr	107 ± 5 #	121 ± 5	120 ± 4	120 ± 4	118 ± 4
SVR, PRU	18.8 ± 1.4 #	9.2 ± .7	8.6 ± .8	8.3 ± .8 *	8.1 ± .8 *
HR X Pa (10^{-3})	10.6 ± 1.1 #	25.7 ± 1.5	28.0 ± 1.2	28.4 ± 1.2 *	28.1 ± 1.3
pHa	7.45 ± .01	7.45 ± .01	7.47 ± .01	7.47 ± .01	7.48 ± .01
pHv	7.40 ± .01	7.35 ± .01	7.38 ± .01	7.39 ± .01	7.40 ± .01
LAv, $mmol \cdot l^{-1}$	.63 ± .12 #	2.02 ± .35	2.05 ± .44	1.83 ± .39	2.62 ± .61
GLv, $mmol \cdot l^{-1}$	3.88 ± .46	3.98 ± .50	3.63 ± .49	3.18 ± .39 @*	2.95 ± .41 @+
Tc, °C	38.6 ± .1 #	39.4 ± .2	39.9 ± .2 *	39.7 ± .3 *	39.7 ± .2 *

[a] Values are means ± SE, n=8 except for SV and HR X Pa where n=7 and for LAv and GLv where n=6. VO_2, O_2 consumption,; Qt, cardiac output; HR, heart rate; SV, stroke volume; a-v02, arterial-mixed venous O2 difference; Pa, mean arterial pressure; SVR, systemic vascular resistance; pHa, arterial pH; pHv, venous pH; LAv, mixed venous lactate; GLv,mixed venous glucose; Tc, core temperature. # Rest mean different from all exercise means ($p<.01$). @ Mean different from rest ($p<.05$). * Mean different from 5 min exercise ($p<.05$). + Mean different from 30 min ($p<.05$).

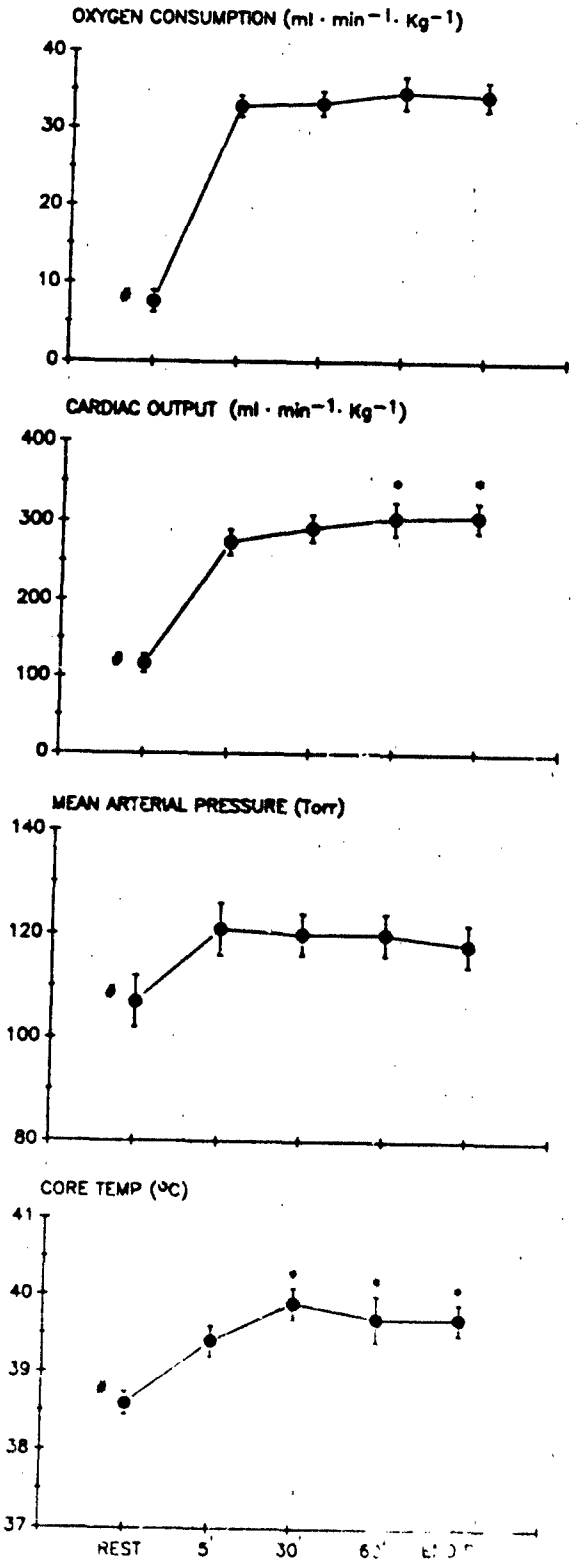

Figure 1. Oxygen consumption, cardiac output, mean arterial pressure and core temperature at rest and during prolonged treadmill exercise. (# rest mean different from all exercise means ($p<.01$); * mean different from 5 minutes of exercise ($p<.05$).

Metabolic and Thermal Responses. For all exercise time points oxygen consumption, mixed venous lactate and core temperature were elevated above resting values (Table 1, Figure 1). Oxygen consumption and mixed venous lactate did not change throughout the exercise bout. However, core temperature increased 0.5°C from 5 min to 30 min of exercise and then plateaued through end exercise. Mixed venous glucose decreased throughout the run. Glucose values at 60 min and end exercise were significantly lower than rest and 5 min, and the end exercise values were lower than 30 min. Mixed venous and arterial pH were unchanged throughout exercise. The arterial-mixed venous oxygen difference increased from rest to 5 min exercise (+5.4 vol%) and then remained elevated above rest throughout the exercise bout. Arterial-mixed venous oxygen difference decreased during exercise but only end exercise was significantly lower than the 5 min value (-.9 vol%).

Table 2. Regional Blood Flow at Rest and During Prolonged Treadmill Exercise in Miniature Swine.[a]

			EXERCISE			
REGION	n	REST	5 min	30 min	END	
Brain	4	84 ± 15	69 ± 16	63 ± 13	76 ± 26	
Lung	5	47 ± 17	77 ± 25	216 ± 66	174 ± 75	
Heart (LV)	4	120 ± 6	263 ± 55	283 ± 36	329 ± 30	@
Kidney (right)	6	417 ± 38	347 ± 52	366 ± 36	234 ± 51	@*+
Kidney (left)	6	413 ± 37	336 ± 49	338 ± 36	231 ± 52	@*+
Adrenal	5	154 ± 59	238 ± 55	328 ± 83	@ 276 ± 56	
Total GI	6	25 ± 4 #	12 ± 2	14 ± 3	11 ± 2	
GI % Qt	6	22 ± 4 #	5 ± 1	5 ± 2	4 ± 1	

[a] Values are means ± SE in $ml \cdot min^{-1} \cdot 100g^{-1}$. LV, left ventricle; GI, gastrointestinal organs; Total GI, $ml \cdot min^{-1} \cdot Kg\ BW^{-1}$; Qt, cardiac output.
Rest mean different from all exercise means ($P<.01$). @ Mean different from rest ($p<.05$). * Mean different from 5 min ($p<.05$). + Mean different from 30 min ($p<.05$).

Regional Blood Flow. Brain blood flow was unchanged, while blood flow to lungs, heart and adrenal gland increased from rest to exercise (Table 2). However, the small number for these organs limited statistical inferences. Right and left kidney blood flows were not altered until end exercise when flow became significantly lower than the rest, 5 min and 30 min time points. Total gastrointestinal blood flow was reduced by 50% from rest to exercise. This represented a change from 22% of total cardiac output at rest to 5% of total cardiac output at 5 min exercise. Total gastrointestinal blood flow was then unchanged throughout the exercise bout.

Table 3. Muscle Blood Flow at Rest and During Prolonged Treadmill Exercise.[a]

		EXERCISE		
MUSCLE	REST	5 min	30 min	END
Rectus Femoris	9 ± 2 #	105 ± 20	88 ± 19	99 ± 19
Biceps Femoris	15 ± 4 #	99 ± 14	110 ± 9	111 ± 12
Semitendinosis	16 ± 6 #	65 ± 11	55 ± 8	58 ± 10
Soleus	14 ± 3 #	46 ± 9	63 ± 6	65 ± 9
Tibialis Anterior	9 ± 2 #	139 ± 18	140 ± 22	133 ± 18
Total Hindlimb	13 ± 3 #	79 ± 10	79 ± 8	83 ± 11
Cremaster	10 ± 4	34 ± 21	36 ± 16	58 ± 17

[a] Values are means ± SE in $ml \cdot min^{-1} \cdot 100g^{-1}$; n=6 except for tibialis anterior where n=5. Total Hindlimb refers to the mean of the 5 hindlimb muscles.
Rest mean different from all exercise means ($P<.01$).

Skeletal Muscle Blood Flow. Blood flow ($ml \cdot min^{-1} \cdot 100g^{-1}$) to four hindlimb muscles exhibited a six fold increase from rest to 5 min of exercise (+66) (Table 3, Figure 2). No further change was observed between 5 min and the 30 min and end exercise time points. The tibialis anterior exhibited the greatest increase in flow (+131) while the smallest change was noted in the semitendinosis (+49). Soleus muscle blood flow increased slightly from five minutes to end exercise (+19;p=.07). Blood flow to the cremaster muscle exhibited an insignificant increase from rest to end exercise.

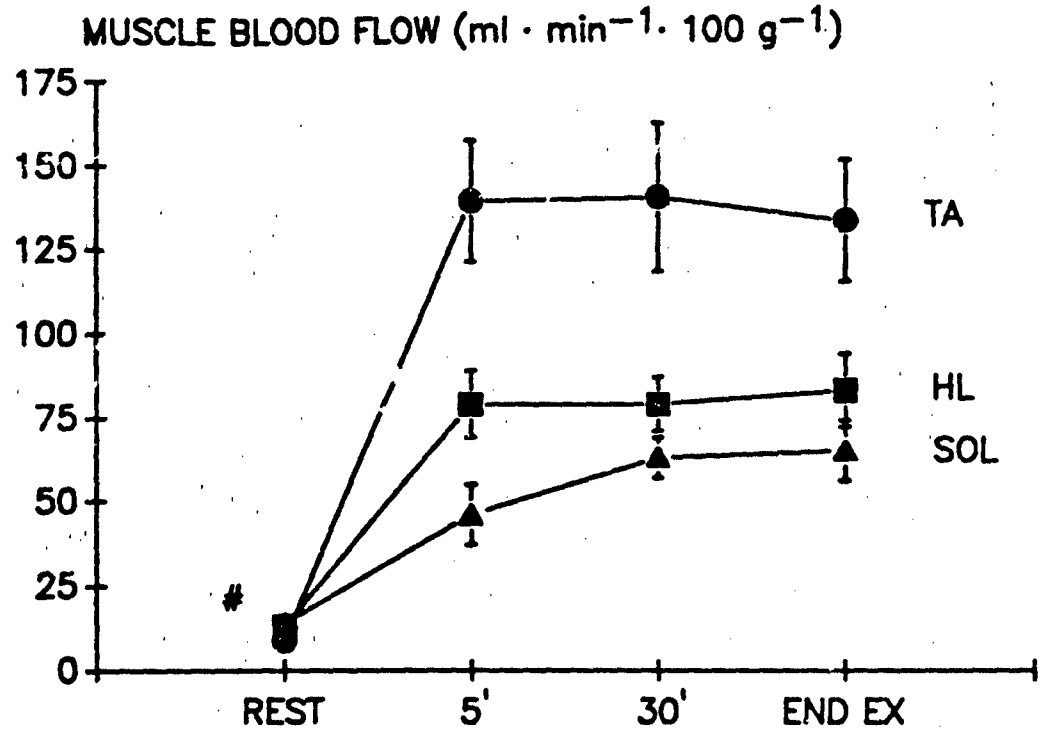

Figure 2. Blood flow to tibialis anterior (TA), combined hindlimb (HL) and soleus (SO) muscles at rest and during prolonged treadmill exercise. (# rest mean different from all exercise means ($p<.01$).

DISCUSSION

Muscle Blood Flow. Hindlimb muscle blood flow remained constant during 100 minutes of treadmill exercise. These findings support observations on humans (1) but contradict previous reports for pigs (3,4) and rats (23). Men exercising at comparable intensity (58% VO_2max), exhibited a constant blood flow to the legs from 40 to 120 minutes of bicycle exercise (1). Systemic and leg oxygen consumption and heart rate (+7 $b \cdot min^{-1}$) were unchanged during this same period, while body temperatures were not measured.

Swine have exhibited marked increases in both forelimb and hindlimb muscle blood flow between 15 and 30 minutes of treadmill exercise at 70% VO_2max (3). This increase in muscle blood flow corresponded to marked increases in cardiac output (+1.2 $l \cdot min^{-1}$), heart rate (+19 $b \cdot min^{-1}$) and colonic temperature (+1.4°C; 41.0°C). Two pigs exercised at 60% VO_2max demonstrated similar muscle blood flow and colonic temperature responses (4). Since external work was held constant and metabolic rate (VO_2) was unchanged, increments in muscle blood flow may be attributed to body temperature and/or factors other than metabolic demand.

Prolonged treadmill exercise in rats elicited a marked increase in hindlimb muscle blood flow between 30 and 54 minutes of exercise (26). Heart rate and mean arterial pressure did not change between these time points and core temperature and oxygen consumption were not measured. Rats have exhibited large increases in colonic temperature (+3°C) reaching 41.8°C during a treadmill run to exhaustion (15). Therefore, temperature may also have contributed to the muscle blood flow response observed during exhaustive exercise in rats (23).

Our observations of constant muscle blood flow and oxygen consumption with limited increases in core temperature, combined with previous muscle blood flow elevations associated with hyperthermia (3,4,23), support a direct link between core temperature, muscle blood flow, and cardiac output. Hyperthermia has been shown to impair physical performance and muscle metabolism in both humans (10,24) and mongrel dogs (19,20). During external cooling experiments, increasing muscle temperatures were associated with higher muscle lactate and lower ATP and CP (19,20). This temperature effect on H^+ and phosphate could mediate a local vasodilation to increase muscle blood flow (20) despite an active sympathetic tone (34). Vasodilation in active muscle could result in a reflex increase in cardiac output to maintain a constant mean arterial pressure (3,19,20,32). Armstrong et al (3), reported that increases in muscle blood flow and core temperature between 15 and 30 minutes of exercise were associated with unchanged oxygen consumption, while the arterial-mixed venous oxygen difference (derived from mean values) declined slightly. These combined observations suggest muscle blood flow may increase dramatically in rats and pigs when core temperature exceeds some threshold value above 39.9°C.

The findings in rats (23) and pigs (3,4) contradict observations in humans and sheep that suggest thermal stress during exercise results in no change or a reduction in muscle blood flow (5,32). Rowell (32) has extensively discussed the potential for vasoconstriction in active muscle while exercising in a hot environment. Studies in man support a mechanism of vasoconstriction in active muscle during moderate and maximal exercise (34). In addition, passive arteriolar tone was shown to increase when core temperature exceeded 37°C (36). The most direct evidence for vasoconstriction was observed in sheep subjected to mild heat stress (40°C) during 30 minutes of treadmill exercise (5). Hindlimb muscle blood flow was reduced when compared with responses under thermoneutral conditions. However, it is important to note that the sheep (5) were exercising at lower core temperatures and lower relative intensities than the pigs (3).

In addition, the pigs in the current study were exercise trained, whereas in previous reports neither the pigs or rats (3,23) were exercise trained. It is possible that repeated exercise and the consequent elevations of core temperature elicits an adaptive response which effectively increases the cooling efficiency of the exercising animal. This adaptive response could include: a coincident decrease in muscle hyperemia and an increase in skin hyperemia to facilitate heat dispersal, an increase in the threshold temperature at which muscle blood flow begins to increase, or a combination of these adaptations. Reflex increases in muscle blood flow in the face of severe hyperthermia may contribute to the hypotension which develops in humans during athletic events (39).

Therefore, the effects of core temperature on muscle blood flow during prolonged exercise remains unclear. Although species differences may be responsible for the divergent blood flow responses, relative heat stress and exercise intensity may be more significant determinants of the observed differences. The pigs were exercised at higher core temperatures and higher relative intensities than the sheep (3,5). Yet, muscle blood flow was increased progressively in the pigs and decreased in the sheep. Our cooling procedures elicited a muscle blood flow response similar to that of humans exercising at a moderate intensity (58% VO_2max) in a neutral environment (29,32). Further work is needed to determine the relationship between hyperthermia and exercise intensity on the muscle blood flow response to prolonged exercise.

Regional Blood Flow. Regional blood flows were dramatically altered with the onset of exercise but tended to plateau and remain constant throughout the exercise bout. In general, the responses were similar to previous reports for exercising swine (2,3). The reduction in kidney blood flow at end exercise was similar to that noted at end exercise in two pigs run to exhaustion at 60% VO_2max (4). This response was consistent with an increased sympathetic drive since kidney blood flow was shown to be inversely proportional to heart rate during exercise (32) and catecholamines increased progressively during prolonged exercise (11,30). Notably, heart rate drifted upward to end exercise in the present study.

Gastrointestinal (GI) blood flow decreased by 50% from rest and then remained constant throughout the exercise bout. However, GI flow did increase slightly between 5 and 30 minutes of exercise. This response was similar to the more dramatic decline and subsequent recovery in GI blood flow observed in pigs (3) and rabbits (16) at the onset of exercise. The slight flow increase at 30 minutes may reflect a flow autoregulation to meet the local metabolic demands of the GI organs. Subsequently, total GI flow declined slightly from 30 minutes to the end exercise time point. A progressive sympathetic drive could explain the latter change since heart rate increased during this period. Blood flow distribution has been linked to sympathetic drive in exercising humans (32). This conclusion was based on the linear inverse relationship observed between heart rate and splanchnic blood flow during exercise. Analysis of our data relating heart rate to total GI blood flow revealed a similar relationship between either heart rate or cardiac output and total GI blood flow. In addition, unpublished observations have indicated that the interval between 30 and 60 minutes of exercise was a critical time for thermal and cardiovascular regulation in our exercising swine model. Core temperature reached a peak and then plateaued or declined during this period.

The relatively constant regional blood flows and arterial-mixed venous oxygen differences we observed suggest that little redistribution of blood flow was occurring during prolonged exercise. However, the increase in heart rate and cardiac output after a plateau in core temperature at 30 minutes probably reflected increased subcutaneous and skin blood flow since skin cooling was effective in maintaining a thermal equilibrium. This is supported by Armstrong et al. (3) who reported an increase in skin blood flow and a

6 fold increase in blood flow to subdermal fat. Although pigs cannot dissipate heat by sweating, we have observed marked skin erythema and elevations in skin temperature when pigs exercise in a neutral environment. Heat stress limited the duration of moderate exercise in a neutral environment unless the animal was cooled by frequent skin wetting and a fan (26). This cooling procedure elicited a core temperature response similar to humans (29,32).

Several problems exist in determining where the additional cardiac output was distributed during prolonged exercise. We were unable to trap enough 15 micron microspheres to accurately measure skin blood flow when the skin was cooled with water (18). However, the elevated lung blood flows at 30 minutes and at end exercise were indicative of increased shunt blood flow (3). The anastomotic vasculature of the skin would promote such shunting (6), particularly when elevated temperature elicits vasodilation (6,15). Thus, reported values for skin blood flow were likely gross underestimations of true flow in exercising swine (3). A similar shunting problem exists in determining whether blood flow increased to tissues that can dissipate heat through panting (3). In contrast to dogs, panting has proven to be an inadequate means of heat dissipation in pigs. This is somewhat surprising because a well developed carotid rete has been described for the pig (25). Finally, subtle changes in blood flow, not reflected by arterial-mixed venous oxygen differences nor detected by microsphere techniques, may have occurred in several organs to account for the increased cardiac output and potential redistribution.

Hemodynamics and Cardiovascular Drift (CVD). During prolonged exercise swine have exhibited a CVD with characteristics different from that of humans (2,3,4,9,32,35). In a neutral environment (20°C), CVD in humans has been described as a downward drift in central venous pressure, stroke volume, pulmonary and systemic arterial pressure resultant from decreased central blood volume, while a compensatory increase in heart rate maintained a relatively constant cardiac output (9,32,35). Sympathetic activity contributed to this response since catecholamines were positively correlated to heart rate drift during prolonged exercise (11,30). Most evidence has indicated that CVD in humans results from the peripheral redistribution of blood flow to the skin for heat dissipation rather than a reduction in cardiac function (28,32).

In contrast, our results for swine demonstrated an increase in cardiac output after 60 minutes of exercise, while stroke volume and mean arterial pressure were unchanged throughout the 100 minute exercise period. Comparable data were reported for pigs exercised for 30 minutes at 70% VO_2max in a neutral environment (3). Heart rate and cardiac output significantly increased between 5 and 30 minutes of exercise, but stroke volumes, derived from the mean cardiac outputs and heart rates, did not change. Surprisingly, the relatively large drop in mean arterial pressure between 5 and 30 minutes (-11 mmHg) was not statistically significant. Although stroke volume did not change, a reduced mean arterial pressure would be consistent with the human response that follows reductions in central blood volume and elevations in skin blood flow to dissipate heat (9,32). In addition, sympathetic activity may be an important CVD factor in swine since marked increases in catecholamines were observed during prolonged submaximal exercise (unpublished observations). These animal studies support observations on humans which suggest the magnitude of CVD is a function of the relative exercise intensity (9,33, 35).

Our observations of stable regional blood flows during prolonged exercise suggest that CVD in swine results from an additive thermal effect, since oxygen consumption, stroke volume and mean arterial pressure were unchanged throughout the exercise bout (Tables 2 and 3). This hypothesized thermal effect is supported by others (3) who reported that marked increases in heart rate and cardiac output corresponded to large elevations in colonic temperature. Mean values from their data revealed correlation coefficients of 0.95 and 0.99 for colonic temperature and heart rate and for colonic temperature and cardiac output, respectively. The increased cardiac output was directed to vasodilated skin and skeletal muscle in pigs exercising at the higher intensities and temperatures (3), whereas the skin was the probable target of increased flow in our animals.

Several differences exist between pigs and humans that may account for the discrepancies in CVD. Central blood volume appears more difficult to maintain during exercise in humans than swine. Quadrupeds have 70% of their blood volume at or above heart level, while humans have 70% below the heart (31). Thus, central hemodynamics should be less effected by peripheral redistribution of a portion of the blood volume. In humans, the essential elevation in cutaneous blood flow to dissipate heat by sweating (32),

decreases venous return and central blood volume, resulting in a reduced stroke volume (9,32). Fluid losses by sweating can exacerbate this loss of blood volume. In contrast, increased blood flow to the skin, carotid rete and active muscle do not appear to compromise the central blood volume in swine. Humans exercising in an upright posture also experience greater hydrostatic pressure on their capacitance vessels resulting in a decreased venous return and stroke volume (31). Furthermore, splenic contraction could maintain total blood volume by counteracting losses in plasma volume and reductions in central blood volume due to increased skin and muscle blood flow (27). Finally, higher circulating catecholamines in swine may elicit a greater heart rate drift during prolonged exercise. This would produce the increase in cardiac output, since stroke volume and presumably central blood volume were maintained throughout exercise.

In addition, an upward drift in oxygen consumption (UDO) during sustained exercise was not clearly demonstrated in our results or in the study of Armstrong et al (3). We observed only a 5% increase in oxygen consumption (VO_2), whi · the swine used by Armstrong et al (3) exhibited a 10% increase in VO_2 during the exercise bout. These values were low compared to the range of 6 to 25% UDO reported for humans exercising in a neutral environment (7,9, 10,14,35). However, the results for swine generally support the importance of relative exercise intensity and body temperature in determining UDO in humans. A greater UDO for the swine used by Armstrong et al (3) was consistent with a higher relative intensity and a higher body temperature than for our animals. Other factors which have been implicated in UDO include: increased work of breathing, decreased respiratory exchange ratio, and increased blood levels of catecholamines and lactate (7,10,14,35). Blood lactate and pH were unchanged throughout the exercise bout in our study and in the study of Armstrong et al. (3). The constant pH reflected the compensatory respiratory alkalosis known to occur in exercising pigs (17). However, a potential role for circulating catecholamines in the modest UDO in swine cannot be discounted.

Therefore, "cardiovascular drift" reflects an additive thermal effect superimposed on the metabolic demands of exercise. In swine, stroke volume and central blood volume are maintained, while a thermal vasodilation in skin and/or active muscle drives cardiac output and heart rate to higher values to maintain a constant blood pressure. In humans, central blood volume and

stroke volume are reduced with the increase in skin blood flow and a compensatory increase in heart rate maintains a constant cardiac output. Exercise intensity and thermal stress interact to determine the magnitude of the CVD.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the technical assistance of Robin Giamela, Paul Kelly, and Abby Murray. Special thanks are extended to Susan Soanes, DVM for her veterinary and technical support. The authors are grateful to Dr. John C. Longhurst, M.D., Ph.D. for the use of his blood gas analyzer and cardiac output computer.

REFERENCES

1. Ahlborg, G. and P. Felig. Lactate and glucose exchange across the forearm, legs and splanchnic bed during prolonged leg exercise. J. Clin. Invest. 69:45-54, 1982.

2. Armstrong, R. B., M. D. Delp , E. F. Goljan and M. H. Laughlin. Distribution of blood flow in muscles of miniature swine during exercise. J. Appl. Physiol. 62:1285-1298, 1987.

3. Armstrong, R. B., M. D. Delp , E. F. Goljan and M. H. Laughlin. Progressive elevations in muscle blood flow during prolonged exercise in swine. J. Appl. Physiol. 63:285-291, 1987.

4. Armstrong, R.B. and M.H. Laughlin. Muscle blood flow-fatigue relationship. In: Saltin, B. (ed.) Biochemistry of Exercise VI. Champaign, Ill.: Human Kinetics Publishers, pp 465-376, 1986.

5. Bell, A.W., J.R.S. Hales, R.B. King and A.A. Fawcett. Influence of heat stress on exercise-induced changes in regional blood flow in sheep. J. Appl. Physiol. 55:1916-1923, 1983.

6. Daniel, P.M. and M.M.L. Prichard. Arterio-venous anastomoses in the external ear. Q. J. Exp. Physiol. Cogn. Med. Sci. 41:107-123, 1956.

7. Dick, R.W. and P.R. Cavanagh. An explanation of the upward drift in oxygen uptake during prolonged sub-maximal downhill running. Med. Sci. Sports Exer. 19:310-317, 1987.

8. Dixon, W. J. (ed). BMDP Statistical Software Manual. Berkley, CA: University of California Press, pp 359-387, 1985.

9. Ekelund, L-G. Circulatory and respiratory adaptations during prolonged exercise. Acta Physiol. Scand.(suppl.) 70:1-38.1967.

10. Fink, W.J., D.L. Costill and P.J. Van Handel. Leg metabolism during exercise in the heat and cold. Europ. J. Appl. Physiol. 34:183-190, 1975.

11. Galbo. H., J.J. Holst and N.J. Christensen. Glucagon and plasma catecholamine responses to graded and prolonged exercise in man. J. Appl. Physiol. 38:70-76, 1975.

12. Gollnick, P.D. and C.D. Ianuzzo. Colonic temperature response of rats during exercise. J. Appl. Physiol. 24:747-750, 1968.

13. Gray, C.G., M.D. McKirnan and F.C. White. Effects of exercise duration and pre-exercise feeding on splanchnic tissue blood flow. (in preparation), 1988.

14. Hagberg, J.M., J.P. Mullen and F.J. Nagle. Oxygen consumption during constant-load exercise. J. Appl. Physiol. 45:381-384, 1978.

15. Hales, J.R.S. Effects of exposure to hot environments on the regional distribution of blood flow and on cardiorespiratory function in sheep. Pfleugers Arch. 344:133-148, 1973.

16. Hales, J.R.S. and J. Ludbrook. Baroreflex participation in redistribution of cardiac output at onset of exercise. J. Appl. Physiol. 64:627-634, 1988.

17. Hastings, A.B., F.C. White, T.M. Sanders and C.M. Bloor. Comparative physiological responses to exercise stress. J. Appl. Physiol. 52:1077-1083, 1982.

18. Heyman, M. A., B. D. Payne, J. I. E. Hoffman, A. M. Rudolph. Blood flow measurements with radionuclide-labeled particles. Prog. Cardiovas. Dis. 20:55-79, 1977.

19. Kozlowski, S., Z. Brzezinska, B. Kruk, H Daciuba-uscilko, J.E. Greenleaf and K. Nazar. Exercise hyperthermia as a factor limiting physical performance: temperature effect n muscle metabolism. J. Appl. Physiol. 59:766-773, 1985.

20. Kruk, B., H. Kaciuba-Uscilko, K. Nazar, J.E. Greenleaf and S. Kozlowski. Hypothalamic, rectal, and muscle temperatures in exercising dogs: effect of cooling. J. Appl. Physiol. 58: 1444-1448, 1985.

21. Laughlin, M.H. and R.B. Armstrong. Muscle blood flow during locomotor exercise. In: Terjung, R.L. (ed). Exercise and Sport Sciences Review, Vol 13. New York: Macmillan Publishing Co., pp 95-136,1985.

22. Laughlin, M.H., R.B. Armstrong, J. White and K. Rouk. A method for using microspheres to measure muscle blood flow in exercising rats. J. Appl. Physiol. 52:1629-1635, 1982.

23. Laughlin, M.H. and R.B. Armstrong. Rat muscle blood flows as a function of time during prolonged slow treadmill exercise. Am. J. Physiol. 244 (Heart Circ. Physiol. 13): H814-H824, 1983.

24. MacDougall, J.D., W.G. Reddan, C.R. Layton and J.A. Dempsey. Effects of hyperthermia on performance during prolonged exercise. J. Appl. Physiol. 36: 538-544,1974.

25. McGrath, P. Observations on the intracranial carotid rete and the hypophysis in the mature female pig and sheep. J. Anat. 124:689-699, 1977.

26. McKirnan, M.D., C.G. Gray, R.J. Giamela, M.J. Buono and C.M. Bloor. Skin wetting (SW) reduces core temperature (T) in exercising swine. Physiologist 1986; 29:115.

27. McKirnan. M.D., C.G. Gray, R.J. Giamela, M.J. Buono and C.M. Bloor. Evidence for splenic contraction in exercising swine. Fed. Proc. 46:679, 1987.

28. Mole, P.E. and R.L. Coulson. Energetics of myocardial function. Med. Sci. Sport Exer. 17: 538-545, 1985.

29. Nielsen, M. Heat production and body temperature during rest and work. In: Hardy, J.D., A.P. Gagge and J.A.J. Stolwijk (eds.), Physiological and Behavioral Temperature Regulation. Springfield, IL: Charles C. Thomas, pp 205-214, 1970.

30. Nielsen, B., G. Sjogaard and F. Bonde-Petersen. Cardiovascular, hormonal and body fluid changes during prolonged exercise. Eur. J. Appl. Physiol. 53:63-70, 1984.

31. Rowell, L.B. Cardiovascular adjustments to thermal stress. In: Handbook of Physiology, Vol III, part 2. The Cardiovascular System. Peripheral Circulation ard Organ Blood Flow. Bethesda, MD: Am. Physiol. Soc., pp 967-1023, 1983.

32. Rowell, L. B. Human Circulation: Regulation During Physical Stress. New York: Oxford University Press, pp 213-256, 363-406, 1986.

33. Rowell, L.B., J.A. Murray, G.L. Grengelmann and K.K. Kraning. Human cardiovascular adjustments to rapid changes in skin temperature during exercise. Cir. Res. 24:711-724, 1969.

34. Savard, G., S. Strange, B. Kiens, E.A. Richter, N.J. Christensen and B. Saltin. Noradrenaline spillover during exercise in active versus resting skeletal muscle in man. Acta Physiol. Scand. 131:507-515, 1987.

35. Shaffrath, J.D. and W.C. Adams. Effects of airflow and work load on cardiovascular drift and skin blood flow. J. Appl. Physiol. 56:1411-1417, 1984.

36. Vanhoutte, P.M. Physical factors of regulation. In: Handbook of Physiology, Vol II. The Cardiovascular System. Vascular Smooth Muscle. Bethesda MD: Am. Physiol. Soc., pp 443-474, 1980.

37. Wilford, D.C. and E.P. Hill. Modest effect of temperature on the porcine oxygen dissociation curve. Respir. Physiol. 64: 113-123,1986.

38. Winer, B.J. Statistical Principles in Experimental Design. New York: McGraw-Hill Book Company, 2nd ed., 625 p, 1971.

39. Wyndham, C.H. Heat stroke and hyperthermia in marathon runners. In: Milvy, P. (ed.) The Marathon: Physiological, Medical, Epidemiological, and Psychological Studies. Ann. N.Y. Acad. Sci. 301:128-138, 1977.

UNCLASSIFIED
SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

1a REPORT SECURITY CLASSIFICATION Unclassified	1b RESTRICTIVE MARKINGS N/A
2a SECURITY CLASSIFICATION AUTHORITY N/A	3 DISTRIBUTION/AVAILABILITY OF REPORT Approved for public release; distribution unlimited.
2b DECLASSIFICATION/DOWNGRADING SCHEDULE N/A	
4 PERFORMING ORGANIZATION REPORT NUMBER(S) NHRC No. 88-32	5 MONITORING ORGANIZATION REPORT NUMBER(S)
6a NAME OF PERFORMING ORGANIZATION Naval Health Research Center 6b OFFICE SYMBOL (If applicable) 60	7a. NAME OF MONITORING ORGANIZATION Commander, Naval Medical Command
6c. ADDRESS (City, State, and ZIP Code) P. O. Box 85122 San Diego, CA 92138-9174	7b. ADDRESS (City, State, and ZIP Code) Department of the Navy Washington, D.C. 20372
8a. NAME OF FUNDING/SPONSORING ORGANIZATION Naval Medical Research & Development Command 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
8c. ADDRESS (City, State, and ZIP Code) Naval Medical Command National Capital Region Bethesda, MD 20814-5044	10. SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO. / PROJECT NO. / TASK NO / WORK UNIT ACCESSION NO.

11. TITLE (Include Security Classification)
(U) PLATEAU IN MUSCLE BLOOD FLOW DURING PROLONGED EXERCISE IN MINIATURE SWINE

12 PERSONAL AUTHOR(S) M. Dan McKirnan; Charles G. Gray; Francis C. White

13a TYPE OF REPORT	13b TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15 PAGE COUNT
Interim	FROM ____ TO ____	1988 AUG 25	

16. SUPPLEMENTARY NOTATION
Prepared in cooperation with the Department of Pathology, University of California, San Diego, School of Medicine.

17 COSATI CODES			18 SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	Prolonged exercise; Muscle blood flow; Thermoregulation; Hemodynamics; Oxygen consumption

19 ABSTRACT (Continue on reverse if necessary and identify by block number)

Cardiovascular, metabolic and thermoregulatory responses were studied in eight male miniature swine during a prolonged treadmill run. Each animal underwent 8 to 10 weeks of exercise training, thoracic surgery and three weeks of retraining prior to the experimental run. This regimen enabled the animals to run at 65% of the heart rate range (~~210-220 b·min^{-1}~~) for approximately 100 minutes. Skin wetting and a fan were used to cool the pigs during the run. Regional blood flow was significantly altered with the onset of exercise; however, hindlimb muscle and total gastrointestinal blood flow were unchanged throughout the exercise period. Compared with five minute values, heart rate and cardiac output were significantly elevated by 17 b·min^{-1} and 31 ml·min^{-1}·kg at 60 minutes and by 20 b·min^{-1} and 33 ml·min^{-1}·kg^{-1} at end exercise, respectively. Core temperatures increased between 5 and 30 minutes of exercise (~~39.4 vs 39.9 °C~~), but then remained unchanged to the end of exercise. Mean arterial pressure oxygen consumption and blood lactate did not change during the exercise bout. These data indicate that limiting increases in core temperature during prolonged exercise was associated with a plateau in active muscle blood flow. The cardiovascular drift observed after the (over)

20 DISTRIBUTION/AVAILABILITY OF ABSTRACT	21 ABSTRACT SECURITY CLASSIFICATION
☐ UNCLASSIFIED/UNLIMITED ☒ SAME AS RPT ☐ DTIC USERS	Unclassified
22a NAME OF RESPONSIBLE INDIVIDUAL Charles G. Gray	22b TELEPHONE (Include Area Code) (619) 553-8453 22c OFFICE SYMBOL 70

DD FORM 1473, 84 MAR 83 APR edition may be used until exhausted
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19. ABSTRACT (continued)
plateau in core temperature probably reflected an increased skin blood flow since cooling procedures effectively limited the thermal stress during prolonged exercise.